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MEMORANDUM

SUBJECT: Review of Laboratory Audit Report for Metolachlor Chronic Rat Study, TOX Chem.#188DD

TO: R. Mountfort, PM#23
Registration Division (TS-767C)

FROM: Gary J. Burin, Toxicologist
Section V, Toxicology Branch
Hazard Evaluation Division (TS-769C)

THRU: William L. Burnam, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769C)

Recommendations: TOX Branch concludes that issues originally triggering the need for a laboratory audit have now been adequately resolved. A rereading of the slides of liver tissue was requested by the Agency in the memo of 2/16/84 from R. Mountfort to Gene Holt of Ciba-Geigy per the suggestion of D.Goldman (Head, Data Integrity Program) in his memo of 1/26/84. When this rereading is complete, it is recommended that a revised estimate of risk be prepared based on the incidence of liver tumors. The audit found no study deficiencies which would preclude this study from being classified as Core Minimum data.
NOTE: The laboratory audit report submitted to TOX Branch was not signed by a representitive of the National Laboratory Audit Program (NLAP). Item 2 in the "Procedures" section of SOP 3050.4 requires that lab audit reports be reviewed by NLAP. This audit therefore apparently did not follow the procedures required by SOP 3050.4. However, NLAP accepts the conclusions of this audit (personal conversation with A. Gross, 9/14/84).

Background: In my memo of 12/14/83, I recommended a laboratory audit be conducted based on conflicting reports of the incidence of liver tumors in the preliminary and final reports for this study. That audit was carried out during May 8-10, 1984 by Ronald R. Ruff, FDA Investigator and M. Adrian Gross, representative of the Office of Pesticide Programs, National Laboratory Audit Program. The lab audit has been reviewed in the context of Standard Operating Procedure 3050.4 and a brief discussion of the findings of that report is presented below.

Discussion: The laboratory audit found that the liver pathology of this study was expedited at the request of the sponsor. The examining pathologist, Dr. Terry A. Jackson, stated to the audit team that initial pathology (reported in the preliminary report) was "gone through hurriedly .... without looking at the pathology sheets." Only routine liver slides were initially examined and tumors that were associated with gross lesions were not included in initial compilation. The examining pathologist also indicated that the initial report may have "overinterpreted" findings and that the diagnoses changed after "literature research and discussion with other pathologists, primarily Dr. Dick Voelker, Head of Pathology, Hazleton Laboratories, Vienna, Virginia...".

The audit did not find any evidence of correspondence with the sponsor on these changes. A selected rereading of slides by Dr. Gross during the course of the audit found that rediagnoses made by the original pathologist were not "unreasonable" (quote from Dr. Gross on p.5 of the lab audit report).

Possible deviations from Good Laboratory Practices regulations were noted but they were of a minor nature which does not effect the validity of the study results. The most significant of the deviations was the lack of retention of raw data (handwritten notes, computer printouts, etc.) for the diagnoses that were originally conducted and entered into the computer. The FDA investigator commented that "FDA surely wouldn't object to this type of raw data retention ... but probably would not require it, with (a) final report signed and dated by the pathologist available." It is noted by this reviewer that the examination of slides during the course of this audit further supported the propriety of the changes in diagnoses.

2